ABSTRACT

Late-stage melanoma is associated with high morbidity and mortality. Classic treatment methods relied on cytotoxic chemotherapy, which is limited by low response rates and significant adverse effects. Recent advances in immunogenetics have led to the advent of important new systemic treatments. This article reviews the latest therapy options for advanced melanoma.

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REVIEW

Systemic Therapies for Late-stage Melanoma

[a]PETER W. HASHIM, MD, MHS; [b]PHILIP FRIEDLANDER, MD, PHD; [a]GARY GOLDENBERG, MD
[a]Department of Dermatology, Icahn School of Medicine at Mount Sinai, New York, New York;
[b]Division of Hematology and Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, New York, New York

MELANOMA IS ONE OF THE most aggressive forms of skin cancer, accounting for the majority of skin cancer mortality. Current estimates project more than 76,000 new cases of melanoma in 2016 and more than 10,000 melanoma-related deaths.[1] Classically, metastatic disease has been associated with five-year survival rates under 20 percent.[2] However, increased understanding of the immunogenetic mechanisms behind melanoma has led to promising new systemic therapies. In this article, the authors review the systemic treatment approaches now available for late-stage melanoma.

CLASSICAL TREATMENT

Previously, treatment for advanced melanoma centered on cytotoxic chemotherapy. Until 2011, the only two systemic therapies approved by the United States Food and Drug Administration (FDA) for the management of stage IV melanoma were dacarbazine and high-dose interleukin 2 (HD-IL-2). Dacarbazine, an alkylating agent, was considered the gold standard of systemic treatment. However, dacarbazine therapy fails to confer a survival benefit, and response rates range from only 5 to 20 percent, with a median response duration of 5 to 6 months.[3] HD-IL-2 is a cytokine-based immunotherapy that requires inpatient administration given its significant toxicity risks, such as capillary leak syndrome, renal failure, and neurologic toxicity. Only 16 percent of patients respond to treatment, but

five percent of treated patients develop durable complete responses.[4] The toxicity profile limits its use to a small subset of patients.

INHIBITORS OF THE MAP KINASE PATHWAY

BRAF inhibition. Targeted therapies underwent rapid expansion following the discovery that melanoma commonly features mutations in the BRAF gene.[5] BRAF is an intracellular protein that regulates the mitogen-activated protein kinase (MAPK) signaling pathway, and activating mutations can lead to unregulated cell proliferation. These BRAF mutations typically involve nucleic acid substitutions for valine at codon 600 and are thus known as BRAF V600 mutations.[6]

Vemurafenib and dabrafenib are BRAF V600 inhibitors currently in use for the treatment of late-stage melanoma. In a Phase 3 clinical trial of 675 patients, vemurafenib was compared to dacarbazine chemotherapy.[7] Patients treated with vemurafenib demonstrated a 48-percent response rate versus five percent with dacarbazine ($p<0.001$). Further analysis showed a median overall survival time in the vemurafenib group of 13.6 months compared to 9.7 months in the dacarbazine group ($p<0.001$).[8] The most common adverse events with vemurafenib were arthralgia, rash, fatigue, squamous cell carcinoma, keratoacanthoma, nausea, alopecia, and diarrhea. In 2011, vemurafenib was approved by the FDA for metastatic and unresectable BRAF-mutated melanoma.

Dabrafenib was similarly compared to dacarbazine chemotherapy in a Phase 3 trial of patients with late-stage melanoma.[9] Dabrafenib was associated with higher response rates (50%) and longer progression-free survival (5.1 months) relative to dacarbazine (5% and 2.7 months, respectively; $p<0.0001$). Noted side effects with dabrafenib were skin-related toxicity, fever, fatigue, arthralgia, and headache. FDA approval was obtained in 2013.

Despite these encouraging results, BRAF inhibitors have been hampered by a high rate of resistance.[10] It is believed to develop owing to reactivation of the MAPK pathway by BRAF-independent mechanisms.[11-13]

MEK inhibition. The identification of BRAF mutations in melanoma has also lead to the targeting of MEK, a protein in the MAPK signaling pathway that lies downstream of BRAF. As resistance to BRAF inhibition partly results from activation of another RAF protein, CRAF, the targeting of downstream MEK can circumvent CRAF-dependent resistance mechanisms. Trametinib is a MEK inhibitor that was FDA approved for BRAF-mutated metastatic melanoma in 2013. Phase 3 trial data showed improved rates of progression-free and overall survival versus standard chemotherapy.[14] However, response rates and progression-free survival were lower than those seen in studies following treatment with a BRAF inhibitor.

Given the same difficulties in resistance as seen with BRAF inhibitors, investigation has shifted toward combination therapy with MEK and BRAF inhibitors. In a study of 247 patients with metastatic melanoma, combined treatment with trametinib and dabrafenib was compared to dabrafenib monotherapy.[15] Median progression-free survival was higher in the combination therapy group (9.4 months) relative to the monotherapy group (5.4 months; $p<0.001$). Combination therapy also led to higher rates of response (76% versus 54% with monotherapy; $p<0.05$). Other studies have reinforced the efficacy advantages of combined MEK and BRAF inhibition, without significant increases in overall adverse events.[16,17]

In a randomized comparison, duel MAPK pathway inhibition with dabrafenib plus trametinib versus BRAF inhibition alone with vemurafenib demonstrated statistically significant increases in response rate, progression-free survival, and 12-month overall survival when using the combination regimen.[17] Currently, two combination regimens, dabrafenib plus trametanib and vemurafenib plus cobimetanib are currently FDA approved for treatment of stage IV melanoma in the presence of a V600 BRAF mutation. The incidence of cutaneous toxicity, such as the development of squamous cell carcinomas,

decreases with combination therapy, as the MEK inhibitor blocks BRAF inhibitor-induced paradoxical activation of the MAPK pathway that develops in cells containing wild-type BRAF and active RAS proteins.

INHIBITORS OF IMMUNE CHECKPOINTS

Immunotherapy—treatment that triggers the body's own immune system to attack cancerous cells—has long been a desired modality for melanoma. Rare spontaneous regressions, the efficacy of interferon alpha in stage III and deep stage II melanoma, and the efficacy of HD-IL-2 in stage IV melanoma all lend support to the notion that certain types of immunomodulation could efficaciously treat advanced melanoma.

CTLA-4 inhibition. Ipilimumab is a monoclonal antibody that inhibits cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), an immune checkpoint protein. CTLA-4 normally serves to downregulate the immune system, and inhibition with ipilimumab can therefore potentiate anti-tumor activity by T cells. In a Phase 3 trial of previously treated patients with advanced melanoma, ipilimumab showed a survival benefit over treatment with a peptide vaccine (overall survival of 10.1 months versus 6.4 months, respectively; $p<0.01$), and two-year survival increased from 14 to 24 percent.[18] Ipilimumab has also demonstrated utility in combination with dacarbazine chemotherapy,

increasing overall survival from 9.1 months with dacarbazine alone to 11.2 months with combination therapy ($p<0.001$), although clinical use of the combination regimen has been limited owing to increased hepatotoxicity.[19]

The FDA-approved ipilimumab for advanced melanoma in 2011. Long-term data from 12 Phase 2 and Phase 3 studies were recently pooled for analysis of treatment outcomes.[20] Of 1,861 patients receiving ipilimumab therapy, the mean overall survival was 11.4 months, with a three-year survival rate of 22 percent. Diarrhea, rash, pruritus, anorexia, and fatigue remain the most common adverse events.

PD-1 inhibition. Another target for immunotherapy is the programmed death 1 (PD-1) pathway. Like CTLA-4, PD-1 serves as an immune checkpoint that regulates the activation of T cells. Targeting of PD-1 on the T cell or its ligand PD-L1, which is expressed in certain melanomas, can produce durable responses in a subset of melanoma patients. Pembrolizumab and nivolumab are monoclonal antibody PD-1 inhibitors that have shown antitumor utility in melanoma.

In 2014, pembrolizumab was approved for patients with advanced melanoma refractory to ipilimumab. In a trial of patients who had previously failed ipilimumab therapy, pembrolizumab provided a 26-percent response rate, with the most common adverse events noted to be fatigue, pruritus, and

rash.[21] Following these results, a Phase 3 study was conducted to directly compare ipilimumab to two different doses of pembrolizumab.[22] The six-month progression-free survival rate was higher for patients receiving pembrolizumab every two weeks (47.3%) and pembrolizumab every three weeks (46.4%) compared to ipilimumab (26.5%; $p<0.001$ for each pembrolizumab group versus ipilimumab). The rate of high-grade immune-mediated toxicity was also lower in the pembrolizumab groups than in the ipilimumab group.

Similar to pembrolizumab, nivolumab has demonstrated efficacy in patients with advanced melanoma following unsuccessful ipilimumab treatment. Among those patients, higher response rates have been seen with nivolumab versus standard chemotherapy.[23] Importantly, nivolumab has demonstrated a clear advantage over chemotherapy for untreated patients without a BRAF mutation.[24] Phase 3 data of 418 patients showed a response rate of 40 percent in the nivolumab treatment group versus 13.9 percent ($p<0.001$) in the dacarbazine chemotherapy group. Rates of drug-related adverse events were comparable between the two groups, although events were generally less severe with nivolumab.

The Phase 3 Checkmate 067 study compared first-line treatment with ipilimumab alone, nivolumab alone, or the combination of ipilimumab plus

nivolumab in 945 patients with stage IV melanoma.[25] Co-primary endpoints were progression-free survival and overall survival (the overall survival data is not yet mature and therefore not yet presented). The median progression-free survival times were 2.9 months for ipilimumab monotherapy, 6.9 months for nivolumab monotherapy ($p<0.001$ compared to ipilimumab), and 11.5 months for combination therapy ($p<0.001$ compared to ipilimumab). However, the rate of high-grade toxicity increased with combination therapy, developing in 55 percent of patients as opposed to 16.3 percent of nivolumab-treated and 27.3 percent of ipilimumab-treated patients.

CONCLUSION

Over the past decade, substantial advances have been made in the treatment of late-stage melanoma. MAPK pathway inhibitors and immune checkpoint inhibitors now surpass standard chemotherapy in response rate and overall survival. It remains to be determined how to best sequence the use of BRAF targeted and PD-1 based immunotherapy regimens in patients with V600 BRAF mutated melanoma. The use of targeted therapies and proper patient selection continues to evolve, holding promise for more specified and effective treatments against advanced disease.

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